



PATENT
Customer No. 22,852
Attorney Docket No. 02481.1403-02

43
2.2.
8/2/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Ulrich Stache et al.

Application No.: 08/897,455

CPA Filed: May 31, 2001

Group Art Unit: 1616

Examiner: B. Badio

RECEIVED

JUL 31 2002

TECH CENTER 1600/2900

For: Corticoid-17,21-dicarboxylic esters and corticosteroid 17-carboxylic ester 21-carbonic esters, processes for their preparation and pharmaceuticals containing these compounds

Commissioner for Patents
Washington, DC 20231

Sir:

Appeal Brief Under 37 C.F.R. § 1.192

In support of the Notice of Appeal filed on May 6, 2002, appellants present in triplicate their Appeal Brief accompanied by a check in the amount of \$320.00 for the fee under 37 C.F.R. § 1.17(c). Appellants also enclose a Petition for Extension of Time to extend the period for filing this Appeal Brief to August 6, 2002.

I. Real party in interest

Hoechst Aktiengesellschaft is the assignee of record in this application. A successor to that company, Aventis Pharma Deutschland GmbH, is the real party in interest.

II. Related appeals and interferences

The appellants, the appellant's legal representative, and the assignee are not aware of any other appeal or interference that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. Status of claims

Claims 11-22 are pending. The Examiner rejected claims 11-17 and withdrew claims 18-22 from consideration. Appellants appeal the rejection of claims 11-17.

The remaining claims will be re-joined for examination upon a finding of allowability of the relevant product claims. The Appendix to this Brief recites the rejected claims.

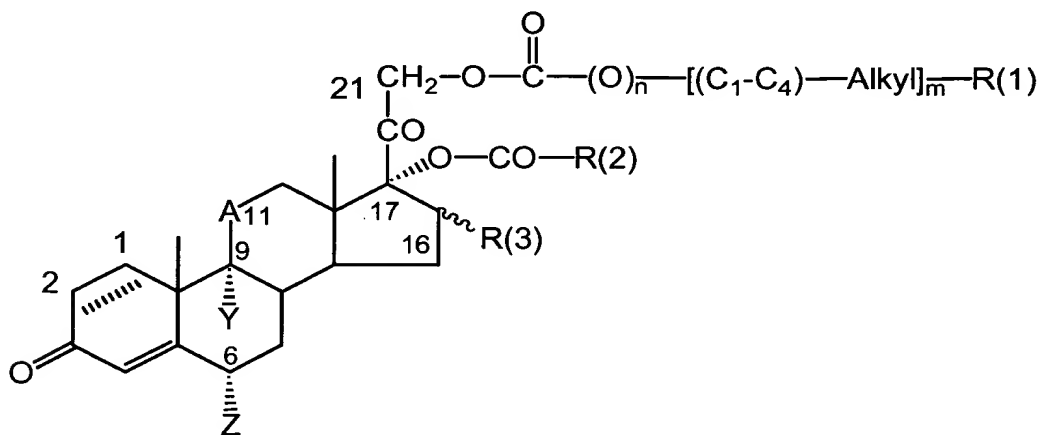
IV. Status of amendments

Appellants did not amend any claims after the Final Office Action of February 4, 2002.

V. Summary of the invention

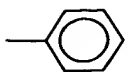
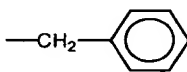
The claims involved in this appeal recite certain compounds, pharmaceutical compositions containing those compounds, and methods of using them. See Specification at page 1, lines 3-6.

Claim 11 recites compounds of formula I:



wherein:

- A is CHOH or CHCl in arbitrary steric arrangement, CH₂, C=O or 9(11) double bond,
- Y is hydrogen, fluorine or chlorine,
- Z is hydrogen, fluorine or methyl,
- R(1) is unsubstituted phenyl or phenyl substituted by one to three substituents selected from the group consisting of methoxy, chlorine, fluorine, methyl, trifluoromethyl, acetamino, acetaminomethyl, t-butoxy, t-butyl, 3,4-methylenedioxy, BOC-amino, amino and dimethylamino,
- (C₁-C₄)-alkyl is saturated,
- n is zero,
- m is 1,

R(2) is linear or branched (C₁-C₈)-alkyl,  or ,

R(3) is hydrogen or α- or β-methyl. The specification supports claim 11 at page 1, line 7 to page 2, line 2.

Claim 12 depends from claim 11 and further defines the substituent R(2) in formula I. The specification supports claim 12 at page 2, line 1.

Claims 13 and 14 depend from claim 11 and further define the substituents A, Y, Z, (C₁-C₄)-alkyl, R(1), R(2) and R(3) in formula I. The specification supports claims 9 and 10 in Examples 23 and 59.

Claim 15 depends from claim 11 and recites a pharmaceutical composition comprising a compound of claim 11 and a pharmaceutically acceptable additive. The specification supports claim 15 at page 13, lines 31-33 and page 15, lines 2-11.

Claims 16 and 17 depend from claim 11 and recite methods for treating dermatoses using a compound of formula I. The specification supports claims 16 and 17 at page 13, lines 20-33.

VI. Issues

I. Whether claims 11-17 would have been obvious under 35 U.S.C. § 103(a) in light of U.S. Patent No. 4,655,971 to Page et al.

II. Whether claims 11-17 would have been obvious under 35 U.S.C. § 103(a) in light of U.S. Patent No. 3,201,429 to Djerassi et al., U.S. Patent No. 3,201,391 to Bowers or U.S. Patent No. 3,133,940 to Oughton et al.

VII. Grouping of claims

Claims 11 and 15-17 stand or fall together. Claims 12, 13 and 14 each stand alone. Applicants explain in the arguments below how claims 11 and 15-17, claim 12, claim 13 and claim 14 are separately patentable.

VIII. Argument

A. Rejection of claims over Page

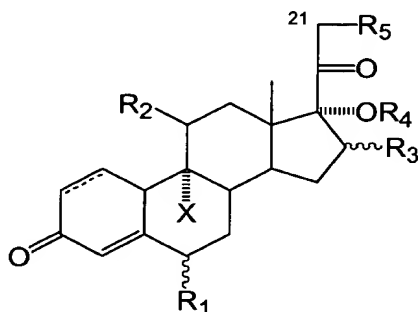
Claims 11-17 stand rejected as obvious under 35 U.S.C. § 103(a) in light of U.S. Patent No. 4,655,971 to Page et al. ("Page"). The Examiner stated that Page teaches 17, 21-dicarboxylic esters of 4-pregnen-3,20-dione having either an oxo,

halogen or hydroxy group in the 11-position and substituents in the 6, 9 and 16 positions that include those recited in the claims.

The Examiner stated that the claimed invention differs from Page by reciting compounds wherein R(1) of claimed formula I is unsubstituted or substituted phenyl. The Examiner stated that Page discloses compounds of its own formula where R₅ of that formula is OC(O)-R", and R" is an alkyl group of 1 to 16 carbon atoms, a phenyl group or an aralkyl group of 7 to 8 carbon atoms such as -(CH₂)₁₋₂-phenyl. The Examiner concluded that appellant's claimed compounds would have been obvious over that disclosure.

1. The appealed claims are not prima facie obviousness over Page

Page discloses a process for preparing compounds of the following formula:



with substituents R₁ to R₅ and X defined in its disclosure. The carbon atom labeled by the appellants with the number "21" corresponds in position to the 21-position carbon atom identified in formula I of the claimed compounds.

Appellants submit that the Page disclosure, taken as a whole, would not have motivated one skilled in the art to make the compounds recited in the claims on appeal. As with any other obviousness determination, the appropriate "point of view" for the analysis must be used. In this regard, obviousness should be viewed through the eyes and mind of one skilled in the art back in time at the moment the invention was made, and without the benefit of the applicant's disclosure. See, e.g., *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Adherence to this point of view avoids the temptation to find an invention obvious by simply piecing together teachings in the prior art in hindsight to approximate that invention. *Id.*

A relevant question for purposes of this appeal is "what compounds would the Page disclosure have motivated one skilled in the art to make?" Using the proper point of view, we do not address that question having knowledge of the claims on

appeal. We instead address the question by looking at the Page disclosure as a whole, including the compounds represented by the formula at col. 1, lines 17-55, specific compounds cited at col. 8, lines 50-59, and the preparation of 28 compounds in Examples 1-28.

The Page description at col. 1, lines 17-55, identifies chemical compounds represented by a core structure having variables at several positions of that structure. Each variable, in turn, is defined in the alternative to include several different possibilities. Some variables, for example variables R₄ and R₅, include several layers of definitions, so a choice of one meaning requires a further choice of sub-meanings, and so on. The definition of R₅, for example, reads as follows:

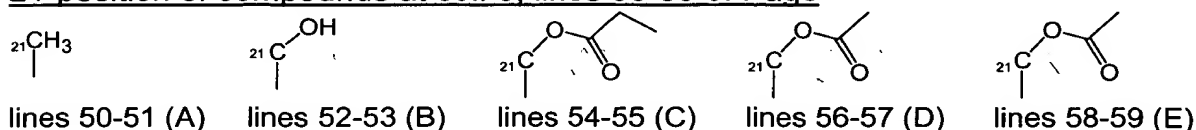
R₅ is hydroxyl or R₆; where
R₆ is hydrogen, one or two halogen atom substituents or OR₇, where
R₇ is an acyl group of the formula R'CO in which R', which can be identical or different to R in the same molecule, is one of the following:
(i) an alkyl group of 1 to 16 carbon atoms, whether straight-chained, branched or cyclic;
(ii) an aralkyl group of 7 to 8 carbon atoms; or
(iii) a phenyl group.

The disclosure at col. 1, lines 17-55, covers an enormous number of compounds reachable through any number of different combinations of definitions of substituents. Would this disclosure have motivated one skilled in the art to make every one of its covered compounds, thereby rendering them all obvious? The answer to that should be "no." The Federal Circuit has stated that "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). The law thus requires something more than a showing of a genus/subgenus relationship between prior art and a claimed invention.

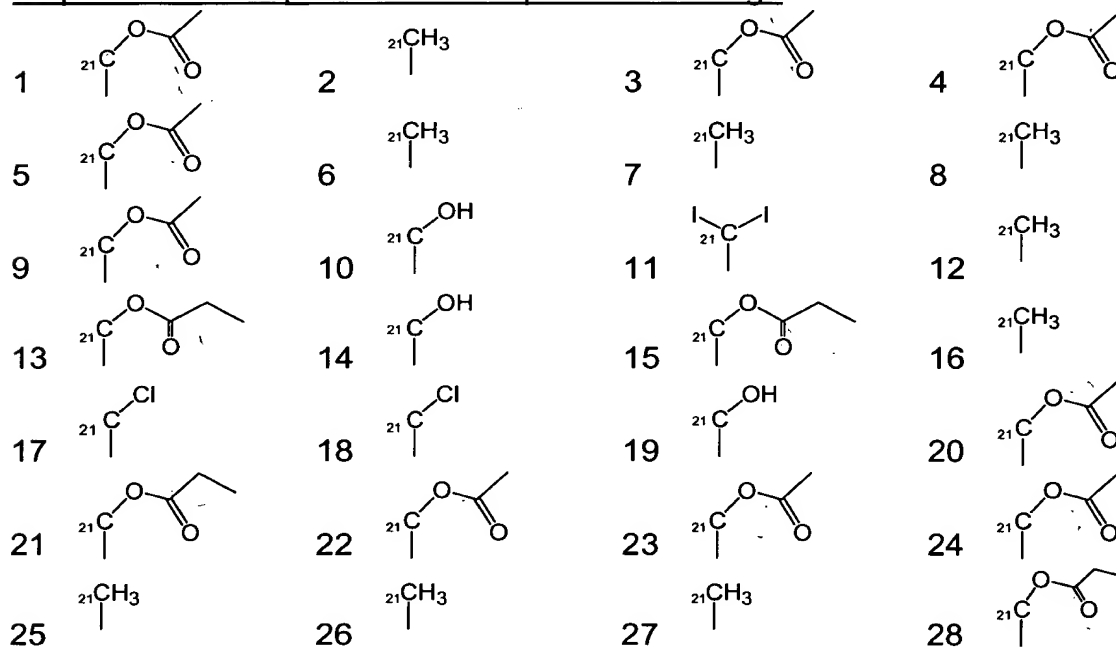
Looking elsewhere in the patent for suggestions of what compounds would have been obvious to make, appellants see no discussion in Page that refers back to the disclosure at col. 1, lines 17-55, or even to the definition of R₅ itself, for example, expressing preferences for particular choices of substituents. Page likewise does not appear to discuss or imply how choices of particular substituents could or would affect the properties of the resulting compounds, either in a positive or negative manner.

Aside from the disclosure discussed above, the compounds listed at col. 8, lines 50-59, and those made in Examples 1-28, also contribute to the Page disclosure as a whole. Without otherwise having guidance as to what compounds within the Page disclosure would have been obvious to make, one skilled in the art would logically have given attention to these examples. To simplify the review of all these compounds, appellants present in the tables below only a portion of their structures, which is that appearing at the 21-position of the compounds:

21-position of compounds at col. 8, lines 50-59 of Page



21-position of compounds in Examples 1-28 of Page

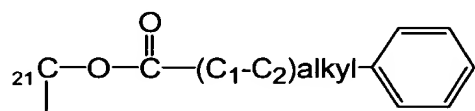


Page's description of the above compounds has value not only for what structures the compounds have, but also for what structures they do not have. A clear pattern emerges showing a focus on certain selections within variable R₅ in the 21-position substituent, while remaining deafly silent on others. For instance, compound "B" and the compounds of Examples 10, 14 and 19 define R₅ simply as hydroxyl. Compound "A" and the compounds of Examples 2, 6-8, 11-12, 16-18 and 25-27 define R₅ as R₆, with R₆ as either hydrogen or one or two halogen

substituents. The remaining compounds define R_5 as R_6 , R_6 as OR_7 , with R_7 being $R'CO$, and define R' as a methyl or ethyl substituent.

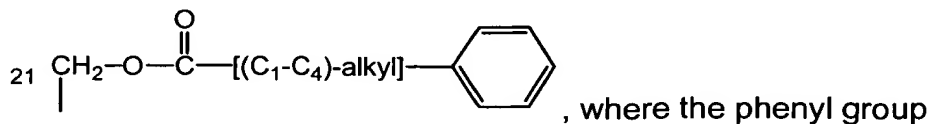
Even when defining R_5 as R_6 , R_6 as OR_7 , with R_7 being $R'CO$, no compounds stray from defining R' as a methyl or ethyl group. This despite the fact that, theoretically, the disclosure at col. 1, lines 17-55 allows R' much greater freedom of being a straight, branched, or cyclic alkyl group of up to 16 carbon atoms, or of being an entirely different group such as the aralkyl group or phenyl group. Indeed, no exemplified compounds contain in the R_5 position any cyclic group of any kind, whether aliphatic or aromatic.

Conspicuously absent in the exemplified compounds, or anywhere else in the disclosure as a whole, is a reasonable suggestion of making compounds with an R_5 substituent shown as follows:



That kind of substituent could result from selecting 1) R_5 as R_6 (instead of as a hydroxyl group), 2) R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents), where R_7 is an acyl group of the formula $R'CO$, and 3) R' as an aralkyl group of 7 to 8 carbon atoms (instead of a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and 4) the aralkyl group as $-(\text{C}_1-\text{C}_2)\text{alkyl-phenyl}$ rather than $-\text{phenyl}-(\text{C}_1-\text{C}_2)\text{alkyl}$. Taken from the proper point of view, looking at the Page disclosure as a whole, this proposal appears, objectively, simply out of place. Yet the Examiner has argued that one skilled in the art would have been motivated to do just that.

By introducing the claimed invention in this discussion now, it becomes evident that perhaps an incorrect point of view, that using hindsight, has been used to find the claimed invention obvious. The present invention contains a substituent at the 21-position carbon atom with following structure:



is optionally substituted.

With the benefit of hindsight from Page, it can be seen that this substituent may be approximated with the detailed selections proposed by the Examiner. Looking only at Page, however, the patent simply does not provide a reasonable suggestion to do so.

In support of the rejection, the Examiner indicated that the skilled artisan would have been motivated to replace the exemplified (i) alkyl group in the formula R'CO of several exemplified compounds with "one of the other two" groups (i.e. (ii) aralkyl or a (iii) phenyl). See page 3 of the Office Action dated February 4, 2002. Replacement of an (i) alkyl group with the (iii) phenyl group would not make the claimed compounds. Instead, it would result in a benzoate group devoid of the [C₁-C₄]-alkyl] element recited in the claims. Moreover, even if one skilled in the art were to choose an (ii) aralkyl group, they still would not necessarily make the -O-CO-[(C₁-C₄)]-phenyl group in the substituent of the invention. An "aralkyl" group also includes substituents such as -O-CO-phenyl-alkyl (in addition to -O-CO-alkyl-phenyl). Page does not appear to suggest a substituent like the appellant's over a different one.

The Examiner's proposal also does not appear to squarely address why one skilled in the art would have been motivated to make that specific switch of substituents at the 21-position of the exemplified compounds, rather any other kind of switch at that position that would result in a compound outside the scope of the invention. The mere possibility of making the proposed substitution is insufficient to justify the rejection, absent a sufficient showing that Page suggested the desirability of that proposal. See *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-84 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."). Appellants do not see such a suggestion in Page or the prior art generally. Instead, for any exemplified compound containing (i) a methyl or ethyl group in R'CO, appellants do not see any more suggestion in Page to follow the Examiner's proposal than to instead choose a different type of alkyl group (for instance a C₃-C₁₆ group), or to choose a phenyl group.

The claimed invention also does not reside simply in the definition of one variable at the 21-position of a compound. The invention as a whole, as defined in claim 11, recites compounds having substituents in a number of locations on the molecule. The Examiner has identified several compounds asserted to "match" all

substituents of the claimed compounds everywhere except at the 21-position, and has argued that it would have been obvious to maintain those substituents on the compounds while modifying the 21-position substituent in a way necessary to derive the claimed compounds.

Appellants do not see the motivation in Page to fix substituents that match with those of the claimed compounds, and switch only a substituent that does not. This "fix and switch" approach has all the hallmarks of a hindsight finding of obviousness. The approach also appears to improperly focus only on what one skilled in the art "could have done," rather than what that person "would have done." See *Ex Parte Marinaccio*, 10 U.S.P.Q.2d 1716, 1717 (Bd. Pat. App. & Intf. 1989) ("the question of obviousness under 35 U.S.C. 103 is not what a routineer could have done but what it would have 'been obvious' for such a person to do."). One skilled in the art could very well have instead chosen to modify those "matching substituents" to make compounds falling outside the scope of the claims. One skilled in the art could also have chosen to begin with compounds having substituents that did not "match" those of the claimed compounds, for instance the compounds of Examples 1 and 28 of Page, thus already starting with compounds quite different from those of the invention. What is of greater relevance is that the Page disclosure, as a whole, simply does not suggest the desirability of the modifications proposed by the Examiner.

In light of the above, the Page disclosure would not have motivated one skilled in the art to make the compounds of any of claims 11-14. Claims 15-17 incorporate the limitations of the compound of claim 11, and should thus stand patentable over Page for the same reasons.

2. Claims 12, 13 and 14 are each separately patentable over Page

Claims 12, 13 and 14 depend from claim 11 and further define substituent R(2) (claim 12) and substituents A, Y, Z, (C₁-C₄)-alkyl, R(1), R(2), and R(3) (claims 13 and 14) in formula I.

In addition to the arguments made above with respect to all claims generally, claim 12 is separately patentable because the Page disclosure did not motivate one skilled in the art to define the 21-position substituent as recited in claim 11 while

simultaneously defining the 17-position substituent as a benzoate or phenylacetate group as recited in claim 12.

Example 19 of Page contains a 17-position benzoate group, but evidence made of record in "Dermatika," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, pp. 322-344 (1992), states that the compound of Example 19 would have been expected to have poor stability. The cited article discusses various properties of compounds, including betamethasone-17 benzoate (Example 19 of Page) and betamethasone 17-valerate. The discussion of betamethasone-17 benzoate begins on column 2 of page 332 of the document and, for stability of the compound, refers to the discussion of betamethasone-17 valerate in column 1 on page 333 (in translation "stability: see betamethasone 17-valerate"). Under the category betamethasone-17 valerate, the document states, in translation from the second column of page 334, last 20 lines, as follows:

"Stability: The compound is unstable to light.
Corticosteroid-17-monoester rearrange easily into 21-monoester in the presence of acids or bases. The 21-monoester of corticosteroids is generally significantly less pharmaceutically active than the respective 17-monoester. Betamethasone-21-valerate has only about 15% of the biological activity of the 17-valerate.
This isomerization occurs particularly quickly in an alkaline milieu. Thus in ointments the 17-valerate is converted to 75% within 5 days under weakly alkaline pH values. Weakly acidic pH-values (for instance the addition of 0.005% phosphoric acid) are stabilizing. The isomerization catalyzed by acids starts significantly only with clearly lower pH- values.

The discussion above would thus tend to discourage, rather than encourage those skilled in the art from using that compound as a starting point for making new compounds.

With respect to claims 13 and 14, the Page disclosure would not have reasonably suggested the simultaneous selection of substituents around the Page formula to make the claimed compounds. For claim 13, the Page disclosure would not have reasonably suggested the simultaneous selection of the following substituents to make the claimed compound:

- X as hydrogen (instead of chlorine or fluorine);
- R₁ as hydrogen (instead of fluorine, chlorine or α - or β - methyl);
- R₂ as hydroxyl (instead of halogen or oxo);

R₃ as hydrogen (instead of α - or β - methyl);

R₄ as an acyl group of the formula RCO, in which R is a phenyl group (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of an aralkyl group);

R₅ as R₆ (instead of as a hydroxyl group),

R₆ as OR₇ (instead of as a hydrogen or as one or two halogen atom substituents),

R₇ as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and
aralkyl group as a C₁-alkyl linking an unsubstituted phenyl to the remainder of the molecule.

For claim 14, the Page disclosure would not have reasonably suggested the simultaneous selection of the following substituents to make the claimed compound:

X as fluorine (instead of hydrogen or chlorine);

R₁ as hydrogen (instead of fluorine, chlorine or α - or β - methyl);

R₂ as hydroxyl (instead of halogen or oxo);

R₃ as β -methyl (instead of hydrogen or α -methyl);

R₄ as an acyl group of the formula RCO, in which R is a phenyl group (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of an aralkyl group);

R₅ as R₆ (instead of as a hydroxyl group),

R₆ as OR₇ (instead of as a hydrogen or as one or two halogen atom substituents),

R₇ as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and
aralkyl group as a C₁-alkyl linking an unsubstituted phenyl to the remainder of the molecule.

These further arguments provide additional bases for reversing the rejection as it applies to claims 12, 13 and 14.

3. *Th unexpectedly superior properties of the claimed compounds would rebut any prima facie showing of obviousness*

Even if the Examiner could have established a *prima facie* case of obviousness, the claimed compounds possess unexpectedly better properties over the prior art that would rebut any such *prima facie* showing.

As explained in the specification of this application, compounds having a 21-aryl ester or 21-hetaryl ester "often exhibit qualities of effect which are clearly superior, as regards the local/systemic ratio of antiinflammatory effect, to those of structurally related corticoid 17,21-dicarboxylic esters or structurally related corticoid 17-alkyl carbonate 21-carboxylic esters which do not carry any aryl or hetaryl group in the 21-acid residue." Specification at page 5, lines 20-29. The class of compounds not having any aryl or hetaryl group in the 21-position obviously include the compounds exemplified in Page.

The claimed compounds "surprisingly" exhibit "a very good ratio of local to systemic antiinflammatory effect, which ratio is often markedly superior . . . to that of known corticoid 17-alkyl carbonate 21-esters, which do not carry any aryl or hetaryl group in the 21-ester radical, such as, for example, 21-ester groups having a 21-alkyl group." Specification at page 13, lines 20-30. Detailed pharmacological testing in support of these statements appears in the specification at page 15, line 12 to page 19, line 16.

The Examiner discounted this evidence as not a true side-by-side comparison with the closest prior art. The one feature all the exemplified Page compounds have in common, however, is the lack of an aryl ester in the 21-position, the very feature distinguished over in the specification. Similar to many exemplified compounds in Page, the reference compound used in the comparative tests in the present specification, prednicarbate, contains an aliphatic group in the 21-position, not an aryl ester. Prednicarbate contains an ethyl group corresponding to group (i) in R₅ of Page, rather than an aralkyl group (ii). Since the Examiner has taken the position that it would have been obvious to switch an alkyl group (i) for an aralkyl group (ii), and since applicants have indicated that compounds having an aralkyl group in the 21-position have unexpectedly better properties than those containing an alkyl group, the comparative tests should be quite relevant to the issues at hand.

B. Rejection of claims over Djerassi, Bowers and Oughton

Claims 11-17 stand rejected under 35 U.S.C. § 103(a) as unpatentable in light of U.S. Patent No. 3,201,429 to Djerassi et al. ("Djerassi") (for claims 11, 12 and 14-17), or U.S. Patent No. 3,201,391 to Bowers ("Bowers") (for claims 11, 12 and 15-17) or U.S. Patent No. 3,133,940 to Oughton et al. ("Oughton") (for claims 11-13 and 15). In support of the rejections, the Examiner argued that the documents teach a number of different acyl groups attached to the 21-position of the compounds, including groups such as phenylpropionyl and phenylacetyl. The Examiner concluded that it would have been obvious to select those groups for the 21-position of the compounds to render the claimed invention obvious.

1. The appealed claims are not prima facie obviousness over the cited documents

Djerassi discloses compounds carrying an -OR' group in the position corresponding to the -O-CO-[(C₁-C₄)-alkyl]-phenyl group of the appealed claims. Djerassi defines R' as hydrogen or a hydrocarbon carboxylic acid acyl group of up to 12 carbon atoms derived from any carboxylic acid having up to 12 carbon atoms, saturated or unsaturated, or straight or branched chain, cyclic or mixed cyclic-aliphatic, substituted or not with methoxy, halogen or other groups. Djerassi at col. 1, lines 44-49. As examples, Djerassi lists acetates, propionates, butyrates, t-butyrate, hemisuccinates, enanthates, caproates, trimethylacetates, benzoates, phenoxyacetates, phenylpropionates, cyclopentylpropionates and β -chloropropionates. Col. 1 at lines 49-53.

The general description in Djerassi at col. 1, lines 44-49, would not have motivated one skilled in the art to use a -O-CO-[(C₁-C₄)-alkyl]-phenyl group as claimed. Furthermore, the phenylpropionate group, listed at col. 1, line 52, appears within a list of 13 various examples of carboxylic acid acyl groups. Djerassi contains no suggestion to choose the phenylpropionate group over any other groups listed in that passage. In addition, the exemplified compounds of Djerassi appear to define R' as acetate or propionate, which indicates a focus on aliphatic groups in that position rather than a suggestion of a phenylpropionate group.

Bowers discloses compounds carrying an -OR group in the position corresponding to the -O-CO-[(C₁-C₄)-alkyl]-phenyl group of the appealed claims.

Bowers defines R as hydrogen or a hydrocarbon carboxylic acyl group containing from 1 to 12 carbon atoms. Bowers states that those acyl groups are derived from hydrocarbon carboxylic acids containing from 1 to 12 carbon atoms and may be saturated or unsaturated, straight chain or branched chain aliphatic, cyclic, cyclic-aliphatic, aromatic and may be substituted by hydroxy, an acyloxy group containing from 1 to 12 carbon atoms, an alkoxy group containing from 1 to 5 carbon atoms or by halogen such as fluorine, chlorine or bromine. Bowers at col. 1, lines 55-61. As examples, Bowers lists the acetate, propionate, butyrate, hemisuccinate, enanthate, caproate, benzoate, trimethylacetate, phenoxyacetate, phenylpropionate and β -chloropropionate group. Col. 1 at lines 62-65.

The general description in Bowers at col. 1, lines 55-61, would not have motivated one skilled in the art to use a -O-CO-[(C₁-C₄)-alkyl]-phenyl group as claimed. Furthermore, the phenylpropionate group, listed at col. 1, line 65, appears within a list of 11 various examples of carboxylic acid acyl groups. Bowers contains no suggestion to choose the phenylpropionate group over any other groups listed in that passage. Like Djerassi, the exemplified compounds of Bowers appear to define R' as acetate or propionate, indicating a lack of motivation to make the claimed invention.

Oughton discloses compounds carrying an -OR₃ group in the position corresponding to the -O-CO-[(C₁-C₄)-alkyl]-phenyl group of the appealed claims. Oughton defines R as "an acyl group." Oughton at col. 2, line 22. As examples, Oughton lists the acyl groups derived from carboxylic acids, such as acetyl, propionyl, benzoyl and phenylacetyl. Oughton at col. 2, lines 23-24. The general term "acyl group" would not have motivated one skilled in the art to use a -O-CO-[(C₁-C₄)-alkyl]-phenyl group as claimed. Furthermore, the phenylacetyl group, listed at col. 2, line 24, appears only as one of several other listed groups. Oughton contains no suggestion to choose the phenylacetyl group over any other groups listed in that passage. In addition, the exemplified compounds in Oughton appear to use groups other than -O-CO-[(C₁-C₄)-alkyl]-phenyl in the 21-position, also indicating a lack of motivation to make the claimed invention.

The state of the art, subsequent to Djerassi, Bowers and Oughton, highlights the lack of motivation to make compounds of any of the appealed claims in light of those disclosures. For this purpose, applicants refer to the teachings of all patents

cited by the Examiner in the Notice of Reference Cited that accompanied the Office Action dated July 25, 1995 (Paper No. 7). None of the patents teaches the 21-position substitution proposed by the Examiner. As the propriety of the Examiner's proposed modifications is determined by the teachings of the prior art as a whole, these patents are relevant to show that the state of the art did not motivate those modifications. Notably, none of these documents opted to use a 21-position phenylpropionate or phenylacetate group, which the Examiner argued to be obvious in light of the Djerassi, Bowers and Oughton disclosures.

U.S. Patent No. 5,026,693 to Villax et al. teaches esters of 9 α -fluoro and chloro-corticosteroids having a substituent Y in the 21-position of the compounds. Villax et al. define Y as, among other things, OR₁, where R₁ may be a benzoyl group (see col. 1, lines 64 and 65). The definition of Y does not include a phenylpropionate or phenylacetate group.

U.S. Patent No. 4,619,922 to Annen et al. teaches 6 α ,16 α -dimethyl corticoids having a substituent Y in the 21-position of the compounds. Annen defines Y as, among other things, benzyloxy (see col. 1, lines 37-39). The definition of Y does not include a phenylpropionate or phenylacetate group.

Having effective filing U.S. dates subsequent to Page, these patents confirm that one skilled in the art, even when in possession of the Page disclosure as well as the disclosures of Djerassi, Bowers and Oughton, would not have been motivated to make the invention on appeal.

The remaining patents, having effective U.S. filing dates subsequent to Djerassi, Bowers and Oughton, also would not have suggested the Examiner's proposed modifications. U.S. Patent No. 4,918,065 to Stindl et al. teaches corticoids having a substituent Z in the 21-position of the compounds. Stindl defines the Z substituent as, among other things, benzyloxy (see col. 1, lines 58-59). The definition of Z does not, however, include a phenylpropionate or phenylacetate group. U.S. Patent No. 4,701,451 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y in the 21-position of the compounds. Annen defines the Y substituent as, among other things, benzyloxy (see col. 1, lines 40-41). The definition of Y does not, however, include a phenylpropionate or phenylacetate group.

U.S. Patent No. 4,645,763 to Annen et al. teaches 6 α -methyl corticoids having a substituent X in the 21-position of the compounds. Annen defines the X substituent as, among other things, acyloxy (see col. 1, lines 27-28) or benzyloxy (col. 8, lines 53-54). The definition of X, however, does not suggest a phenylpropionate or phenylacetate group. U.S. Patent No. 4,567,172 to Kamano et al. teaches 6 α -methylprednisolone derivatives having a substituent -O-R¹ in the 21-position, where R¹ may be -CO-R³, and R³ may be a phenyl group (see col. 2, lines 40-63). This disclosure does not suggest compounds having a phenylpropionate or phenylacetate group, but instead at best a benzyloxy group. Finally, U.S. Patent No. 4,555,507 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y in the 21-position of the compounds. Annen et al. defines the Y substituent as, among other things, benzyloxy (see col. 1, lines 38-39). The definition of Y does not include a phenylpropionate or phenylacetate group.

In light of the above, the prior art as a whole would not have motivated one skilled in the art to make the claimed compounds. Appellants agree with the Examiner that the legal issue raised in these rejections is not how many patents there are with similar compounds, but whether the prior art would have made the claims on appeal obvious. The appellants present this discussion to show that those skilled in the art, when in possession of the disclosures cited by the Examiner, would not have been motivated to make the claimed invention. Absent a *prima facie* showing of obviousness, this rejection should be reversed.

2. Claims 12, 13 and 14 are not *prima facie* obviousness over the cited documents

In addition to the arguments made above with respect to all claims generally, claim 12 is separately patentable because none of the three cited documents would have motivated one skilled in the art to define the 21-position substituent as recited in claim 11 while simultaneously defining the 17-position substituent as a benzoate or phenylacetate group as recited in claim 12. Certainly none of the exemplified compounds in any of those documents make such a combination or even comes close to such a combination.

Claim 13 is patentable in its own right because the Oughton disclosure would not have reasonably suggested the simultaneous selection of the following substituents for its compounds:

R₁ as hydroxyl (rather than as an oxygen atom);

R₃ as phenylacetyl (rather than any other "acyl group," including the acetyl, propionyl and benzoyl groups);

R₄ as benzoyl (rather than a hydrogen atom or any other "acyl group," including the acetyl, propionyl and phenylacetyl groups);

R₂ as hydrogen (rather than halogen).

Lastly, claim 14 is patentable in its own right because the Djerassi disclosure would not have reasonably suggested the simultaneous selection of the following substituents for its compounds:

Y as hydroxyl (rather than as hydrogen or a keto group);

A 9-position fluorine in place of hydrogen;

A 6-position hydrogen in place of methyl;

R' as phenylpropionate (rather than hydrogen and any other possible carboxylic acid acyl group of up to 12 carbon atoms, including acetates, propionates, butyrates, t-butyrate, hemisuccinates, enanthates, caproates, trimethylacetates, benzoates, phenoxyacetates, cyclopentylpropionates and β -chloro-propionates);

R as benzoate (rather than hydrogen and any other possible carboxylic acid acyl group of up to 12 carbon atoms, including acetates, propionates, butyrates, t-butyrate, hemisuccinates, enanthates, caproates, trimethylacetates, phenoxyacetates, phenylpropionates, cyclopentylpropionates and β -chloro-propionates).

These further arguments provide additional bases for reversing the rejection as it applies to claims 12, 13 and 14.

3. The unexpectedly superior properties of the claimed compounds would rebut any prima facie showing of obviousness

As explained earlier, compounds having a 21-aryl ester or 21-hetaryl ester "often exhibit qualities of effect which are clearly superior, as regards the local/systemic ratio of antiinflammatory effect, to those of structurally related corticoid

17,21-dicarboxylic esters or structurally related corticoid 17-alkyl carbonate 21-carboxylic esters which do not carry any aryl or hetaryl group in the 21-acid residue." Specification at page 5, lines 20-29. The class of compounds not having any aryl or hetaryl group in the 21-position obviously include the compounds exemplified in the documents cited in the rejection. In fact, a large majority of the compounds exemplified in those documents contain aliphatic alkyl groups in the corresponding 21-position, not aryl groups.

The claimed compounds "surprisingly" exhibit "a very good ratio of local to systemic antiinflammatory effect, which ratio is often markedly superior . . . to that of known corticoid 17-alkyl carbonate 21-esters, which do not carry any aryl or hetaryl group in the 21-ester radical, such as, for example, 21-ester groups having a 21-alkyl group." Specification at page 13, lines 20-30. Detailed pharmacological testing in support of these statements appears in the specification at page 15, line 12 to page 19, line 16.

The Examiner discounted this evidence as not a true side-by-side comparison with the closest prior art. The compounds exemplified in the cited documents, however, lack an aryl ester in the 21-position, the very feature distinguished over in the specification. Similar to many exemplified compounds in the cited documents, the reference compound used in the comparative tests in the present specification, prednicarbate, contains an aliphatic alkyl group in the 21-position, as a propionate group, and not an aryl ester. Since applicants have indicated that compounds having an aralkyl group in the relevant 21-position have unexpectedly better properties than those containing an alkyl group, the comparative tests should be quite relevant to the issues at hand.


IX. Conclusion

In light of the comments made above, appellants respectfully request reversal of the pending rejections. Please grant any further extensions of time required to enter this Appeal Brief and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 25, 2002

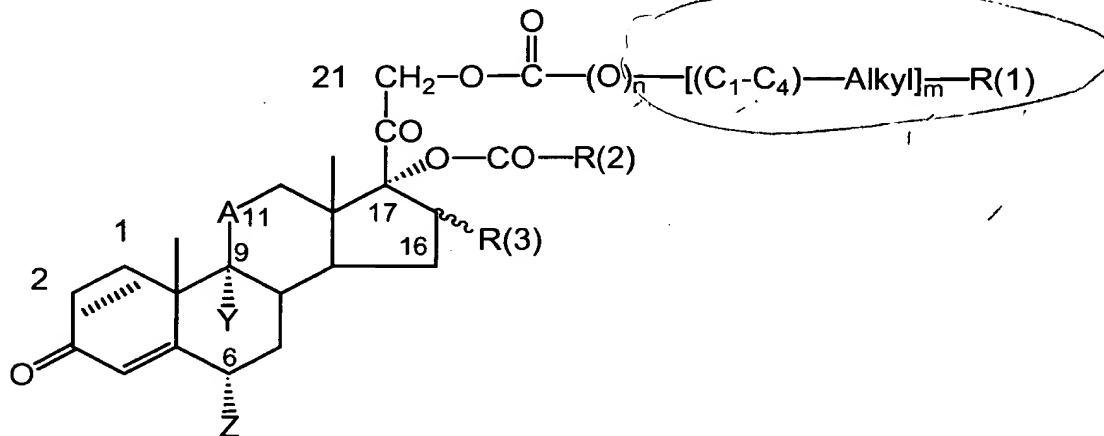
By: 
Steven J. Scott
Reg. No. 43,911

Post Office Address (to which
correspondence is to be sent)

Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005
(202) 408-4000

Appendix Reciting Claims Involved in the Appeal

11. A corticoid 17,21-dicarboxylic ester or corticosteroid 17-carboxylic ester 21-carboxylic ester of the formula I



wherein:

A is CHOH or CHCl in arbitrary steric arrangement, CH₂, C=O or 9(11) double bond,

Y is hydrogen, fluorine or chlorine,

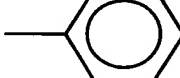
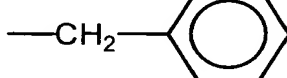
Z is hydrogen, fluorine or methyl,

R(1) is unsubstituted phenyl or phenyl substituted by one to three substituents selected from the group consisting of methoxy, chlorine, fluorine, methyl, trifluoromethyl, acetamino, acetaminomethyl, t-butoxy, t-butyl, 3,4-methylenedioxy, BOC-amino, amino and dimethylamino,

(C₁-C₄)-alkyl is saturated,

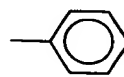
n is zero,

m is 1,

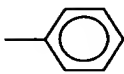
R(2) is linear or branched (C₁-C₈)-alkyl,  or ,

R(3) is hydrogen or α- or β-methyl.

12. A compound as claimed in claim 11, wherein R(2) is

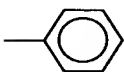


13. A compound as claimed in claim 11, wherein A is CHOH, Y is hydrogen, Z is hydrogen, (C₁-C₄)-alkyl is C₁-alkyl, R(1) is unsubstituted phenyl, R(2) is



, and R(3) is hydrogen.

14. A compound as claimed in claim 11, wherein A is CHOH, Y is fluorine, Z is hydrogen, (C₁-C₄)-alkyl is C₁-alkyl, R(1) is unsubstituted phenyl, R(2) is



, and R(3) is β -methyl.

15. A pharmaceutical composition, which comprises an effective amount of at least one compound as claimed in claim 11, together with a pharmaceutically acceptable additive.

16. A method for treating dermatoses, which comprises applying to skin in need of the treatment an effective amount of at least one compound as claimed in claim 11.

17. A method as claimed in claim 16, wherein the dermatoses are inflammatory and allergic.